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(57) Abstract

The present invention relates to a multi–layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent–releasing multi–layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.

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MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE

The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example and to a method of manufacturing such a sleeve.

More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve for encompassing an expandable device, such as a stent, to be introduced into a body canal, such as a blood vessel for example.

Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.

Disorders of body canals, such as coronary arteries for example, are generally caused or provoked by the presence, on the inner walls of the canal, of deposits which cause strictures or stenoses in said canal.

The treatment of such disorders generally calls for the use of an inflatable device, such as a dilatation catheter for example, for restoring the normal section of flow of the canal at the level of the stenosis. In a certain number of cases, the result is further optimised through implantation of an expandable device in order to provide support to the vessel wall.

Such expandable devices are well-known in the field of medicine for implantation in blood vessels, biliary ducts, or indeed other similar organs of the living body. They generally fall into two categories : those known as self-expandable prostheses, and those which require a forced expansion with the aid of a balloon for example ; both types are commonly known as stents in the cardiovascular field. Such expandable devices are used to maintain, open, or dilate tubular structures or to support tubular structures

that are being anastomosed.

Although stents have in general shown to be very effective in restoring canal patency by virtue of a scaffolding role which counteracts the phenomenon of remodelling, the implantation of a stent provokes substantial vascular injury which in some cases leads to clinical symptoms and the necessity for medical reintervention. Subacute stent thrombosis remains a threat post-stent implantation in spite of improvements in drug regimens applied post-intervention. More importantly, the healing response of the arterial wall post implantation engenders the proliferation of smooth muscle cells and consequently the formation of neointimal hyperplasia which leads to inner stent-restenosis, a condition for which no satisfactory solution has yet been found.

Methods of inhibiting thrombus formation has been the subject of much research and publications in the literature. The object of the majority of this research has been into coated stents.

One of the methods described uses the concept of coating a stent with a polymer. Furthermore, the local delivery of therapeutic agent(s) using stents has centred around two concepts :

i) directly coating the stent wires with a therapeutic agent or a therapeutic agent-polymer combination (Bailey *et al.*, Circulation, 1990, 82: III-541 ; Cavendar *et al.*, Circulation, 1990, 82 :III-541) ; and

ii) incorporating a therapeutic agent into a stent that was constructed not of metal but of a biodegradable polymer (Murphy *et al.*, J. Invasive Cardiol., 1991, 3 : 144-148).

The major advantage of directly coating a device, such as a stent wire, with a therapeutic agent or a therapeutic agent-polymer combination is the low quantity of therapeutic agent necessary because the therapeutic agent is released close to the indwelling device.

Most efforts were focused upon directly coating the metal stent wires with a polymer. This polymer is usually placed directly on the stent

(for example by the method disclosed in EP-A-0 797 963, which involves dipping the stent in a solution of a polymer in a solvent, followed then by the evaporation of the solvent) or is covalently bound to the metal. The polymer is bonded to or contains an anticoagulant compound. Most coated stents currently under development use heparin as the active ingredient. One of the more effective polymer coated stent is Biogold (van der Giessen *et al.*, Circulation, 1990, 82 :III-542). Biogold and other coated stents have not however completely prevented arterial thrombosis. This is probably due to the cracking of the polymer as the stent is expanded during deployment, saturation of the anticoagulant binding sites on the stent, and/or the inadequacy of heparin as an anticoagulant in the prevention of arterial thrombosis and/or too small quantities of therapeutic agent in comparison with the total surface of arteries wall covered by the stent. It is because of these inadequacies associated with polymer coatings directly applied to stent wires that there remains a great need to effectively prevent vascular response at the site of the stent.

US 5,383,928 (EMORY UNIVERSITY, United States of America) entitled "Stent sheath for local therapeutic agent delivery" discloses a stent sheath for local therapeutic agent delivery. More specifically, the patent discloses a sheath for encompassing at least a portion of a stent to locally deliver a drug to an arterial wall or lumen into which the stent has been inserted, comprising a polymer and a drug incorporated within the polymer, the polymer sheath encompassing at least a portion of the stent and having a thickness to allow controlled release of the drug.

The major disadvantage of the sheath according to this prior art document resides in the fact that in order to change the therapeutic agent or adapt the therapeutic agent release rate incorporated therein, it is necessary to change the entire sheath itself (thickness, nature of polymer(s) etc.). Consequently, the whole mechanical properties of the entire sheath would also be changed.

The principal aim of the present invention therefore is to solve the technical problem consisting in providing a sleeve for encompassing an expandable device for introduction into a body canal of a patient, said sleeve being adaptable in every way to the needs of the patient's canal in question.

More specifically, in order for said sleeve to be adaptable in every way to the needs of the patient's canal in question, the sleeve, preferably of polymeric nature, would have to meet the following requirements in being :

(a) bio-compatible, it causing little or no response from the body canal in question;

(b) non-biodegradable, it being required to remain without any change in its properties in contact with the body canal in question for a specified amount of time;

(c) sufficiently elastic to be expandable, when wet with a body fluid for example, it being capable of being expanded to the dimensions of the body canal in question; but,

(d) sufficiently inelastic so as not to recoil from its expanded state;

(e) of a sufficient mechanical strength so as it tears neither under expansion nor in the expanded state;

(f) of such a chemical nature that it is optionally able not only to be either coated or impregnated with any therapeutic agent(s) whatsoever in need of which the patient's body canal in question may be, said therapeutic agent(s) being capable of treating either a disorder of a body fluid flowing through the patent's body canal or a disorder of a body canal wall, or, more importantly, both, but furthermore of such a chemical nature that the rate of release of said therapeutic agent(s) be controlled at a rate pre-determinable according to the needs of the patient's body canal in question,

(g) in the case where the therapeutic agent(s) are impregnated in

the sleeve, the sleeve would have to be of a thickness pre-determinable according to the amount of therapeutic agent(s) it is desired to be released i.e. the thicker the sleeve, the more therapeutic agent(s) it may contain and release, and, finally,

(h) able to optionally encompass an expandable device, a stent for example, it being possible for said expandable device to be either embedded within said sleeve, or disposed radially and internally with respect to said sleeve, according to the needs of the patient.

The inventors of the present invention have carefully addressed the above-mentioned requirements and have been able to provide a solution to the present technical problem in the form of a sleeve which is comprised not of just a mixture of polymers, but a system of polymer layers.

More importantly, the sleeve in accordance with the present invention is comprised of a system of polymer layers which are actually able to adhere together without affecting the elasticity and mechanical properties of the sleeve resulting therefrom in any way whatsoever, and which thus provides a solution to the present technical problem in the form of a sleeve having highly advantageous properties over those of the prior art in a totally unexpected way.

Thus, according to a first aspect, the present invention provides a sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that predetermined mechanical properties of said sleeve be provided.

According to a second principal aspect, the present invention provides a sleeve for encompassing an expandable device for introduction

into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.

Advantageously, the mechanical properties of the resulting sleeve are thus governed by the at least one biocompatible, non-biodegradable elastic polymer layer, and the excellent biocompatibilty of said sleeve are conferred thereto by the hydrogel inner and/or outer layers. Moreover, said sleeve, when wet with body fluid at 37°C is able to expand according to the needs of the patient's body canal, this being without any unsticking of the layers comprising said sleeve.

Within the context of the present invention the term:

"non-biodegradable" is understood as meaning a polymer which does not fail the "environmental stress cracking", or " ESC". ESC has been attributed to biochemical and cellular interactions at the surface of the implanted material causing polymer chain cleavage. This may result in surface fissuring followed by deep cracking associated with considerable biodegradation of the polymer, resulting in loss of mechanical strength;

"biocompatible" is as defined by the US Pharmacopeia and refers to a polymer which successfully passes the USP Class V1 plastics testing; and

"hydrogel" is understood as meaning a material which is hydrophilic

in nature and which exhibits the characteristic macromolecular structure of a gel. A gel is best described as a continuous three-dimensional network that is held together by chemical or physical bonds. Sufficient interstitial space exists within the network, and water molecules can become trapped and immobilised, filling the available free volume. Gels can be divided into two major categories based on the types of bonds that comprise them. These include chemical gels and physical gels.

Advantageously, the above-mentioned sleeve is characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a material selected from the group consisting of polyurethane, silicone, and latex. The material needs to have a good elasticity that is an elongation of at least 500% (PU tensile strength 7,500 psi elongation 500%, latex tensile strength 85 kg/cm^2 elongation 700%, silicone tensile strength 1310, elongation 1000%) and a good flexure resistance in vivo (no oxidation of the material even if the sleeve is stretched).

The nature of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

Also advantageously, the above-mentioned sleeve is characterised in that said hydrogel outer and inner layers independently comprise at least one hydrophilic polymer selected from the group consisting of polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

Such hydrophilic polymers are particularly preferred within the context of the present invention because they possess a capacity to act as a vehicle for the therapeutic agent(s) useful for treating a body canal, and, more importantly, because they are able, once mixed with other polymers

or cross-linked, to release the therapeutic agent(s) at a rate which is pre-determinable by easy selection of the thickness of said film or layer, and the ratio of therapeutic agent with the hydrogel.

The nature of the composition of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

An example of a particularly preferred hydrophilic polymer that may be used within the context of the present invention is poly (N-vinylpyrolidone), especially when the biocompatible, non-biodegradable elastic polymer layer is made of polyurethane. A particularly suitable material is produced under the trade name Hydromer and is made by the interaction of poly-vinylpyrrolidone (PVP) with one of several isocyanate prepolymers.

According to an advantageous embodiment of the present invention, the above-mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

According to a further advantageous embodiment of the present invention, the above mentioned sleeve is characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

Within the context of the present invention, the term "therapeutic agent" is understood as meaning any compound which has a pharmacological effect.

Particularly advantageously, the above-mentioned sleeve is characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin compound, a platelet receptor antagonist, an anti-thrombin antibody, an

anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof ; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor antagonist, a transcriptional activator, a translational promoter, or a combination thereof ; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against growth factors, a bifunctional molecule consisting of a growth factor and a cytotoxin, and a bifunctional molecule consisting of an antibody and a cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a vasodilating agent, an agent which interferes with endogenous vasoactive mechanisms, or a combination thereof ; or a smooth muscle inhibitor, such as an agent which modulates intracellular calcium binding proteins, a receptor blocker for contractile agonists, an inhibitor of the sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor agonist, an antimitotic agent, an immunosuppresive agent, a protein kinase inhibitor, or a combination thereof ; or a combination thereof.

According to a third principal aspect, the present invention provides a system for introduction into a body canal, characterised in that it comprises an expandable device and a multi-layered sleeve in accordance with the present invention.

According to an advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is embedded within said biocompatible, non-biodegradable elastic polymer layer.

According to a further advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is disposed radially and internally with

respect to said hydrogel inner layer.

According to a particularly advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is a stent.

The sleeve length may be of shorter or longer length then the expandable device optionally encompassed therein, or of course be of the same length.

According to a fourth aspect, the present invention provides a system which is characterised in that it is intended to be introduced into a body canal comprising a canal wall and a lumen through which a body fluid flows and in that said sleeve comprises a hydrogel inner layer which can contain one or more therapeutic agents capable of treating a disorder of said body fluid, and a hydrogel outer layer which can contain one or more therapeutic agents capable of treating a disorder of said body canal wall.

According to a fifth aspect a particularly advantageous method of manufacturing the sleeve of the invention comprises dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

Various alternative methods of manufacture are described in more detail below in the Examples.

The invention will be better understood and other objects, characteristics and advantages thereof will become more clearly apparent from the following explanatory description referring to the attached schematic drawings, which are given solely by way of non-limiting examples illustrating two preferred embodiments of the invention, and in which:

Figure 1 is a longitudinal schematic view showing a system comprising a stent and a multi-layered sleeve according to a first preferred embodiment of the invention, in which said stent is disposed radially and

internally with respect to said multi-layered sleeve, represented in a body canal;

Figure 1A is a view in cross section of Figure 1;

Figure 2 is a longitudinal schematic view, similar to Figure 1, illustrating a second preferred embodiment of the sleeve according to the invention, in which the stent is embedded within the biocompatible, nonbiodegradable elastic polymer inner layer of said sleeve;

Figure 2A is a view in cross section of Figure 2.

In all Figures 1A, 1B, 2A, and 2B,

1 represents the at least one, optionally therapeutic agent(s)-containing, hydrogel outer layer of the multi-layered sleeve in accordance with the present invention,

2 represents the at least one biocompatible, non-biodegradable elastic polymer layer of the multi-layered sleeve in accordance with the present invention,

3 represents the expandable device for introduction into a body canal; and

4 represents at least one, optionally therapeutic agent(s)-containing, hydrogel inner layer of the multi-layered sleeve in accordance with the present invention.

The multi-layered sleeve is advantageously manufactured by a dipping process in which a mandrel is successively dipped in a solution in which there are different components, polymers and solvents. This successive dipping process builds up the different layers of the sleeve, as detailed above, and also ensures that, should an expandable device such as a stent be incorporated, such a device may, if required, be fully embedded in the finished sleeve. Layers which are required to be thicker than one dipping can provide are made by multiple dippings of the same component until the required thickness has been built up. Each dipping step consists in vertically immersing the mandrel in the different solutions

using an automatic soaking machine. The thickness of membrane laid down at each dipping step is controlled by the following parameters:

the rate of insertion into the solution;

the time resident in the solution;

the rate of withdrawal from the solution;

the concentration of the solution.

After each dipping step, the coated mandrel is subject to curing. During curing the following phenomena occur:

Cross-linking of the principal components.

Solvent evaporation.

It is important to ensure that the cross-linking is complete and that all of the solvent has been evaporated from the different layers. To ensure this, the temperature at which the curing takes place, and the duration of curing, may be controlled. At the completion of the processing, the sleeve is removed from the mandrel.

The following examples give detail of the technique which is followed, it being understood that these are provided as an illustration of the technique used to prepare the sleeves according to the present invention and are in no way intended to limit the scope of the invention.

EXAMPLE I:

PREPARATION OF A SLEEVE WITH A HEPARIN-CONTAINING HYDROGEL INNER LAYER

A 10% solution of polyurethane in N,N-dimethylacetamide is prepared. A 1.25 mm mandrel is dipped in the solution. The dipped mandrel is cured at 75°C in an oven for 20 minutes.

The mandrel is dipped again in the solution. The mandrel is cured again at 75°C for 20 minutes. The mandrel is then dipped in the hydrophilic solution containing the heparin (3% of heparin benzalkonium chloride solution + PVP) and is then cured at 60°C for 30 minutes. The sheath is

retrieved from the mandrel and reversed (i.e. turned inside out, or transposed). The membrane is inserted onto a translumenal prosthesis (stent).

The translumenal prosthesis is placed onto a 3.5 PTCA catheter and is inflated at the 3.5 mm diameter.

The translumenal prostheses are then tested for anti-clotting properties in comparison with the translumenal prosthesis without the hydrogel inner layer.

The inner surfaces were then extracted in human plasma at 37°C for 7, 10, 21 or 28 days and then tested for anti-clotting properties. The results obtained are shown in the Table.

TABLE

SAMPLE	CLOTTING TIME (minutes)
Uncoated sample	12
coated sample without extraction of plasma	did not clot
coated sample with 7 days extraction in plasma	did not clot
coated sample with 10 days extraction in plasma	did not clot
coated sample with 21 days extraction in plasma	24
coated sample with 28 days extraction in plasma	20

EXAMPLE 2:

PREPARATION OF A SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

polyvinylpyrrolidone l g

nitrocellulose 0.12 g

ethanol 9 ml

dimethylformamide 3.0 ml

ethyl acetate 0.4 ml

A 1.25 mm diameter mandrel is dipped in the polyurethane solution.

The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel is then dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

The sleeve is retrieved from the mandrel, reversed and put again onto the mandrel.

The mandrel is dipped again in the hydrophilic solution and cured for 30 minutes at 75°C.

The sleeve is retrieved from the mandrel, cut and inserted onto a translumenal prosthesis (stent).

The translumenal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

EXAMPLE 3:

PREPARATION OF STENT INCLUDING SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS (According to Figure 2)

A 10% solution of polyurethane in N,N-dimethylacetamide is prepared.

A 1 mm diameter mandrel is dipped in the solution. The dipped mandrel is cured at 75°C in an oven for 20 minutes. The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

The sleeve is retrieved from the mandrel, reversed and put back on the mandrel.

The translumenal prothesis (stent) is put onto the mandrel and the sleeve and is crimped on it.

The mandrel is dipped again in the polyurethane solution. The mandrel is cured again at 75°C for 20 minutes.

The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

The translumenal prothesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

EXAMPLE 4:

PREPARATION OF A SLEEVE WITH HYDROGEL OUTER LAYER

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

polyvinylpyrrolidone 1 g

nitrocellulose 0.12 g

ethanol 9 ml

dimethylformamide 3.0 ml

ethyl acetate 0.4 ml

Two mandrels (A and B) of 1.25 mm in diameter are dipped in the polyurethane solution. The dipped mandrels are cured at 75°C in an oven for 20 minutes. The mandrels are dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel A is then dipped in the hydrophilic solution and cured for 30 minutes at 75°C.

The sleeve is retrieved from the mandrels. A tensile test is done on the two wet sleeves at 37°C. The two curves are identical up to 1000% elongation.

EXAMPLE 5:

PREPARATION OF A SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. A 2 mm, mandrel is dipped in a first hydrogel solution.

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes. The first and second hydrophilic solutions may or may not be the same solution.

EXAMPLE 6:

PREPARATION OF A STENT INCLUDING SLEEVE WITH HYDROGEL INNER AND OUTER LAYERS (According to Figure 1)

A 18% solution of polyurethane in N,N-dimethylacetamide is prepared. Two hydrogel solutions are prepared as inner and outer layers.

The translumenal prosthesis (stent) is put onto a 2 mm mandrel.

The mandrel is dipped in a first hydrogel solution.

The dipped mandrel is cured at 70°C in an oven for 60 minutes.

The mandrel is then dipped in the polyurethane solution, and is then cured at 70°C for 60 minutes. The mandrel is dipped in a second hydrophilic solution and cured at 70°C for 60 minutes.

The stent sleeve is retrieved from the mandrel.

The translumenal prosthesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

The advantages of the sleeves according to the invention are that they provide a sheath to improve the surface of the stent and/or to locally deliver therapeutic agent(s) to an arterial wall or lumen. The covered translumenal prosthesis can be used advantageously in a coronary artery after an angioplasty procedure but also to treat a prostate cancer whereby

a chemotherapeutic agent is released directly into the urethra via the translumenal prosthesis implanted as an endoluminal prosthesis. Since a sleeve according to the present invention is used for delivering the therapeutic agent(s) and not the translumenal prosthesis itself the quantities of therapeutic agent are bigger than can be achieved with a coated translumenal prosthesis.

CLAIMS

1. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic, hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic. layer being such that pre-determined mechanical properties of said sleeve be provided.

2. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.

3. The sleeve according to claim 1 or 2, characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a synthetic material selected from the group consisting of polyurethane, silicone, and latex.

4. The sleeve according to any one of claims 1 to 3, characterised in that said inner and outer synthetic hydrogel layers independently comprise at least one hydrophilic polymer selected from the group consisting of

polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

5. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said biocompatible, non-biodegradable elastic polymer layer is between 25 and 60 μm, preferably between 30 and 40 μm.

6. The sleeve according to any one of claims 1 to 4, characterised in that the thickness of said hydrogel inner and outer layers is, in the dry state, between 7 and 20 μm .

7. The sleeve according to any one of claims 2 to 6, characterised in that said therapeutic agent(s)-containing hydrogel inner layer contains one or more therapeutic agents capable of treating a disorder of a body fluid.

8. The sleeve according to any one of claims 2 to 7, characterised in that said therapeutic agent(s)-containing hydrogel outer layer contains one or more therapeutic agents capable of treating a disorder of a body canal wall.

9. The sleeve according to any one of claims 2 to 8, characterised in that said therapeutic agent(s) is (are) selected from the group consisting of an anticoagulant, such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, an antithrombin compound, a platelet receptor antagonist, an anti-thrombin antibody, an anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof ; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor agonist, a transcriptional activator, a translational promoter, or a combination thereof ; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against

growth factors, a bifunctional molecule consisting of a growth factor and a cytotoxin, and a bifunctional molecule consisting of an antibody and a cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a vasodilating agent, an agent which interferes with endogenous vasoactive mechanisms, or a combination thereof; or a smooth muscle inhibitor, such as an agent which modulates intracellular calcium binding proteins, a receptor blocker for contractile agonists, an inhibitor of the sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor agonist, an antimitotic agent, an immunosuppresive agent, a protein kinase inhibitor, or a combination thereof; or a combination thereof.

10. A system for introduction into a body canal, characterised in that it comprises an expandable device and a multi-layered sleeve according to. any one of claims 1 to 9.

11. The system according to claim 10, characterised in that said expandable device for introduction into a body canal is embedded within said biocompatible, non-biodegradable elastic polymer layer.

12. The system according to claim 10, characterised in that said expandable device for introduction into a body canal is disposed radially and internally with respect to said inner hydrogel layer.

13. The system according to any one of claims 10 to 12, characterised in that said expandable device for introduction into a body canal is a stent.

14. The system according to any one of claims 10 to 13, characterised in that it is intended to be introduced into a body canal comprising a canal wall and a lumen through which a body fluid flows and in that said sleeve comprises a therapeutic agent(s)-containing hydrogel inner layer which contains one or more therapeutic agents capable of treating a disorder of said body fluid, and a therapeutic agent(s)-containing hydrogel outer layer which contains one or more therapeutic agents capable of treating a disorder of said body canal wall.

15. A method of manufacturing a sleeve as claimed in any one of claims 1 to 9, said method comprising dipping a mandrel successively into different solutions in order to build up said layers, said dipped mandrel being subject to curing inbetween each successive dipping.

16. A method as claimed in claim 15 in which said mandrel is first dipped in a polymer solution and thence cured to form said elastic polymer layer, thence dipped into a hydrogel solution and thence cured to form a hydrogel layer.

17. A method as claimed in claim 16 wherein, in order to form said polymer layer, multiple dippings into said polymer solution, with curing inbetween, are carried out until the desired thickness for the polymer layer is achieved.

18. A method as claimed in either one of claims 16 or 17 in which, following the formation of said hydrogel layer, the sleeve is removed from the mandrel, turned inside out, and put back again onto the mandrel, following which the coated mandrel is dipped in a hydrogel solution, which may or may not be the same as the first-mentioned hydrogel solution, and is then cured.

19. A method as claimed in claim 18 wherein, after the sleeve has been replaced on the mandrel after having been turned inside out, a stent is placed over the mandrel and sleeve prior to the dipping step.

20. A method as claimed in claim 15 in which said mandrel is first dipped in a hydrogel solution and thence cured to form a hydrogel layer, is then dipped into a polymer solution and is thence cured to form a polymer layer and is then dipped into a hydrogel solution which may or may not be the same as the first-mentioned hydrogel solution, followed by curing.

21. A method as claimed in claim 20 wherein prior to the first dipping in a hydrogel solution, a stent is placed over the mandrel so that said hydrogel layer is formed over the stent and mandrel.

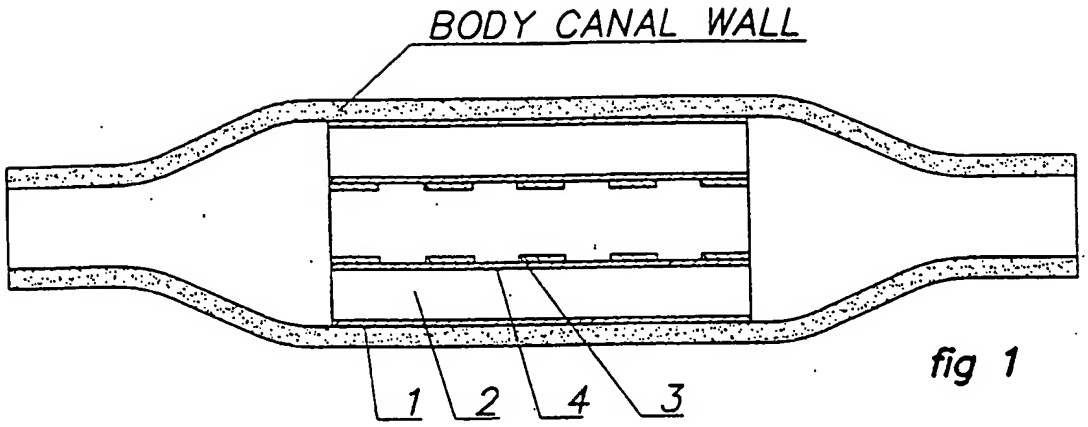

fig 1

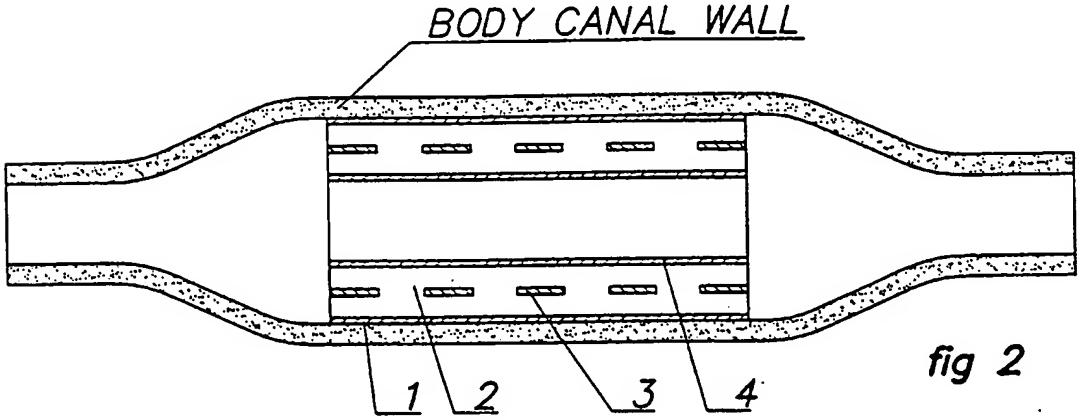

fig 2

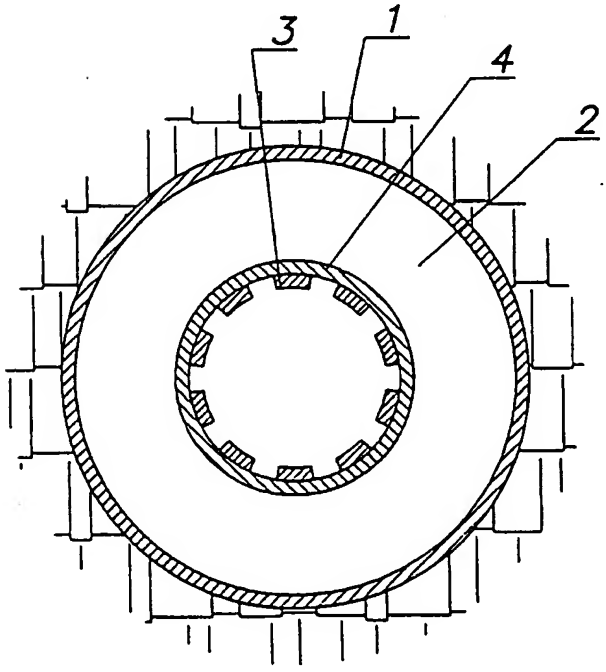

fig 1A

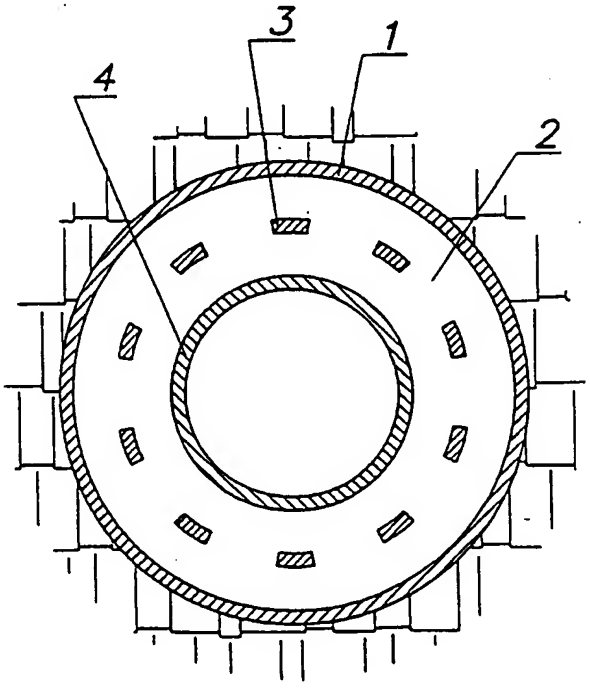

fig 2A

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 99/07156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L B05D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 95 29647 A (SCIMED LIFE SYSTEMS INC) 9 November 1995 (1995-11-09) figures 6,10,12 page 4, line 26 - line 30 page 5, line 9 - line 17 page 5, line 24 - line 27 page 6, line 18 - line 26 page 7, line 16 -page 8, line 20 page 13, line 23 -page 14, line 2	1-13 15-21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 December 1999	21/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thornton, S

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INTERNATIONAL SEARCH REPORT

Inte Jonal Application No
PCT/EP 99/07156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	page 6, line 19 -page 7, line 3 figures claims	1-9
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